

# De-Escalating Axillary Surgery in Node-Positive Breast Cancer Treated with Neoadjuvant Systemic Therapy

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## Keywords

Node-positive breast cancer · Neoadjuvant systemic therapy · Axillary surgery

## Abstract

**Background:** There is a trend towards de-escalating axillary staging and treatment in breast cancer patients. On account of neoadjuvant systemic therapy, node-positive breast cancer patients can achieve a pathological complete response of the axilla. It is hypothesized that these patients do not benefit from an axillary lymph node dissection (ALND), and thus may be spared the risk of severe post-surgical morbidity. In an effort to omit standard ALND, less invasive axillary staging procedures are being implemented to establish response-guided treatment. However, it is unclear which less invasive staging procedure is most accurate, and long-term data are missing with regard to their oncologic safety. **Summary:** This article provides an overview of the literature on currently used less invasive axillary staging procedures, the accuracy and feasibility of these procedures in clinical practice, important issues concerning axillary treatment, and issues to be addressed in ongoing or future studies. **Key messages:** More evidence is needed regarding the safety of replacing standard ALND by less invasive axillary staging procedures in terms of long-term prognosis. These less invasive staging procedures not only serve

to select patients who may benefit from treatment de-escalation, but also to select patients who may benefit from treatment escalation.

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## Introduction

Since the 1990s, there has been a trend towards less invasive staging and treatment strategies of the axilla in breast cancer patients. The axillary lymph node dissection (ALND), which is associated with the risk of severe post-surgical morbidity such as lymphedema and paraesthesia [1, 2], is no longer standard of care in node-negative breast cancer (cN0) patients. On account of important trials such as NSABP B-32, the sentinel lymph node biopsy (SLNB) has replaced standard ALND, based on a comparable survival and regional control, and less morbidity [3–5]. Even if the SLNB is positive (with a maximum of two positive nodes), ALND can be safely omitted in patients who receive breast-conserving therapy and adjuvant treatment [6–10]. It is therefore questioned if performing an SLNB is of added value in these patients. As a result, trials such as INSEMA (NCT02466737), SOUND, and BOOG 2013-08 are currently investigating whether SLNB can be safely omitted in cN0 patients who are treated with breast-conserving therapy [11, 12].

In node-positive breast cancer (cN+) patients, attempts to de-escalate axillary staging and treatment are also made, yet in a less progressive manner. Neoadjuvant systemic therapy (NST) is increasingly used in these patients, which enables assessment of *in vivo* response to systemic therapy, and has the benefit of downsizing the primary tumour, thereby making breast-conserving therapy more often feasible [13, 14]. NST can also downsize axillary disease and result in a pathological complete response of the axilla (i.e., axillary-pCR). Axillary-pCR rates vary depending on breast cancer molecular subtype and can be as high as 74% in HER2-positive patients [15–19]. Patients who achieve an axillary-pCR are not expected to benefit from ALND. On that account, less invasive axillary staging procedures have been introduced in an effort to establish response-guided treatment, thereby omitting ALND in case of an axillary-pCR. However, it is unclear whether it is safe to omit standard ALND in cN+ patients treated with NST, with regard to long-term prognosis. A lack of consensus concerning regional management in these patients has resulted in a large variety of axillary staging and treatment strategies worldwide.

### Currently Known Less Invasive Axillary Staging Procedures

In order to replace standard ALND, a less invasive axillary staging procedure has to be highly accurate. In other words, the chance that axillary residual disease is missed should be as low as possible (i.e., low false-negative rate [FNR] and high negative predictive value [NPV]). The SLNB was the first procedure to be suggested for less invasive axillary staging that could potentially lead to omitting standard ALND in cN+ patients treated with NST. Trials such as SN FNAC, SENTINA, and ACOSOG Z1071 have shown that the SLNB has unacceptable FNRs and a NPV that does not exceed 86%, indicating that residual disease is missed in 1 of 6 patients with a negative SLNB [17, 20–23]. Suggested methods to improve the FNR are the use of immunohistochemistry, dual tracer, and excision of at least 3 SLNs. Even though the latter did have a statistically significant effect on the FNR in a meta-analysis [17], in clinical practice it is often not feasible to remove 3 SLNs. Hence, although successful in cN0 patients, SLNB is not accurate enough as stand-alone procedure in cN+ patients who are treated with NST, possibly because NST and axillary metastases result in an altered lymph drainage. In 2010, the MARI-procedure was introduced, in which an axillary lymph node metastasis was marked with a radioactive iodine seed before NST, and excised after NST with the use of a gamma probe [24, 25]. This strat-

egy overcomes the issue of potentially altered lymph drainage. Although an FNR of 7% was achieved, its NPV was comparable to that of the SLNB. The definition of axillary-pCR varied between these studies (i.e., counting isolated tumour cells as either negative or positive), which should be kept in mind when comparing their results. A promising alternative is combining SLNB and excision of a marked positive axillary lymph node (i.e., Targeted Axillary Dissection, TAD). Even though the evidence is limited to a few small cohort studies [26–29], it is plausible that a higher accuracy is achieved when these strategies are combined, since the marked lymph node appears not to be the SLN in 23.0–35.2% of cases [26, 28, 29]. Preliminary results of the RISAS trial (i.e., combining SLNB and MARI-procedure) seem to verify the accuracy of TAD in a multicentre cohort of 227 patients [30]. Final results of the RISAS trial and GANEA-3 (NCT03630913) will have to be awaited to decide which staging procedure is most accurate [31]. In the meantime, other factors are being explored in an effort to further optimize TAD, in particular the type of marker used and the most appropriate timing for marker placement, which both will be discussed below.

### Targeted Axillary Dissection: Markers

Given the idea that a combination procedure is most accurate for axillary staging after NST, and radioactive iodine seeds are not allowed to be used for this purpose in various countries, several variations of TAD have been investigated. Mostly in small and retrospective cohorts, markers such as wire [32–34], carbon ink [35–38], magnetic seeds [39, 40], and clips [29] have been used, which all have certain benefits and downsides with regard to identifying the marked lymph node. Wire, carbon ink, and clips are non-radioactive and less expensive than radioactive iodine and magnetic seeds, and therefore often preferred options for TAD. However, a wire needs to be placed just prior to surgery, which can result in planning difficulties, and it can cause discomfort since patients have to keep their arm in a certain position to prevent the wire from dislocating, which is another risk of this procedure. Carbon ink can spread beyond the marked lymph node, which can result in unnecessary removal of more lymph nodes, thus increasing the risk of post-surgical morbidity. Apart from this, clips are not always easily localized with ultrasound, which may indicate the need for a mammography or computed tomography scan. All these drawbacks can result in the inability to perform TAD. The magnetic seed is more or less comparable to the radioactive iodine seed, since a probe (e.g., Senti-mag) is used to localize the marked lymph node. Yet,

the magnetic seed can give an artefact on the magnetic resonance imaging, which may complicate the assessment of response to NST. In a currently recruiting, multicentre, prospective registry study (NCT04580251), the magnetic seed, radioactive iodine seed, and carbon ink are compared with regard to reliability of the individual markers. Outcomes such as marker migration, the ability to localize the marker, and the success rate of excision of the marked lymph node are assessed. The study is expected to be completed in 2023. Other factors that future research should focus on regarding identifying the most optimal marker are patient satisfaction and cost-effectiveness.

### Targeted Axillary Dissection: Timing

Timing also varies amongst different TAD procedures, as it can either be applied as a one-step procedure or a two-step procedure. In a one-step procedure, the metastatic lymph node is marked with a definitive marker (e.g., radioactive iodine seed in the MARI-procedure) before NST, and is identified and excised at the time of surgery. In a two-step procedure, the metastatic lymph node is clipped before NST, and only after NST a definitive marker is placed adjacent to the clip, to enable identification and excision of the clipped lymph node at the time of surgery. It can be considered that a two-step procedure is more prone to fail, and moreover, patients have to undergo an additional procedure. In a study by Nguyen et al. [41], placement of a radioactive iodine seed in the clipped node was possible in only 80% of the patients. Hartmann et al. [34] also reported a failure rate of 20% for localizing the clipped node in a study in which wire-placement was attempted. In the recently published multicentre Senta trial, wire-placement in the clipped node was not successful in 22% of the patients [28]. In almost half of the cases, this was due to the fact that the clipped node could not be identified on ultrasound. The procedure seemed to be associated with a learning curve, since failure rates were less in more experienced participating centres. In the ILLINA trial, the additional procedure was omitted, and intra-operative ultrasound was used to guide excision of the clipped node, which had a high success rate [29]. Another method to overcome the need for an additional procedure after NST is currently being investigated in the Magellan trial (NCT03796559). In this trial, a magnetic seed is placed prior to NST instead of after NST. Since the different TAD procedures were mostly explored in small and retrospective cohorts, and not directly compared within a trial, evidence is lacking to determine the most optimal TAD procedure for establishing response-guided treatment.

### Response-Guided Axillary Treatment and Long-Term Prognosis

Response to NST is a strong prognostic indicator, with pCR being associated with improved survival [42, 43]. Patients who achieve a pCR of the breast as well as the axilla have the most favourable prognosis, but also patients with breast-only or axilla-only pCR have improved prognosis [44]. Several studies reported that axillary-pCR seems to have a greater effect on prognosis than breast-pCR [44, 45]. These findings are the major driver of developing response-guided treatment approaches. Less invasive axillary staging procedures were initially proposed to omit unnecessary ALND in patients with axillary-pCR. However, it does not only enable omission of ALND in selected patients, it also serves as a procedure to identify patients who may benefit from additional treatment. In case of residual disease, selected patients may benefit from ALND and/or regional radiotherapy. Almahariq et al. [46] conducted a retrospective study to assess whether the extent of axillary surgery affected prognosis in cT1-3N1 patients with residual disease in 1–3 lymph nodes who were treated with regional radiotherapy. In a matched cohort, 304 patients who only underwent SLNB had significantly lower survival than the 1,313 patients who underwent ALND, with estimated 5-year overall survival rates of 71 and 77%, respectively ( $p = 0.006$ ). In a subgroup of luminal A or B tumours with residual disease in a single lymph node, SLND and ALND were associated with similar overall survival rates of 85 and 82%, respectively. In a retrospective study by Laot et al. [47], it was suggested that depending on breast cancer molecular subtype, the extent of residual axillary disease may affect prognosis in a different manner. Prognosis was similar for patients with residual disease in up to 3 lymph nodes and patients with axillary-pCR in case of luminal breast cancer, whereas residual disease in 4 or more lymph nodes was associated with decreased prognosis. In patients with HER2+ or triple-negative (TN) breast cancer, prognosis was not only decreased in patients with 4 or more positive lymph nodes but also in patients with 1–3 positive lymph nodes [47]. Apart from additional regional treatment, patients with residual disease can also benefit from additional systemic treatment such as TDM-1 in HER2+ patients and capecitabine in TN patients, as was demonstrated in the Katherine and Create-X trials, respectively [48, 49]. Residual disease may be limited to the axilla; therefore, it is of utmost importance to accurately identify axillary disease to provide patients with the appropriate adjuvant treatment.

Several ongoing trials are assessing the value of adjuvant ALND and/or regional radiotherapy in cN+ patients treated with NST. The NSABP-B51/RTOG 1304 and ATNEC trials include patients with axillary-pCR

(NCT01872975, NCT04109079), the Alliance A011202 and TAXIS trials include patients with residual disease (NCT01901094, NCT03513614), and the MINIMAX registry study includes both patients with an axillary-pCR and those with residual disease (NCT04486495). Furthermore, the 3-year follow-up results of response-guided axillary treatment according to the MARI protocol [50] (i.e., use of PET-CT as pre-NST staging, followed by the MARI procedure as post-NST staging) in a cohort of 272 patients were presented at EBCC 2020 [51].

## Conclusion

In cN+ patients who are treated with NST, there is an undesired large variety in axillary staging and treatment strategies worldwide. TAD seems to be most accurate for axillary staging in cN+ patients who are treated with NST. While the results of validation trials are awaited, more evidence is needed regarding the safety of replacing standard ALND by less invasive axillary staging in terms of long-term prognosis. Moreover, clinicians should keep in

mind that less invasive axillary staging procedures not only serve to select patients who may benefit from treatment de-escalation, but also to select patients who may benefit from treatment escalation.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

S.d.W. prepared the manuscript and is the corresponding author. J.S. prepared the manuscript. M.V.P. and M.S. are members of the writing committee. L.K. supervised S.d.W. and J.S. All authors have contributed to the study's conception and design, and have read and edited the manuscript. All authors approved the final manuscript.

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